Altered cell wall composition as part of the mechanism of antibiotic resistance - in staphylococci and pneumococci.

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A common and novel feature of several antibiotic resistance mechanisms appears to be the direct involvement of cell wall muropeptide chemistry.The ability of bacterial cells to alter the carboxy terminus of wall precursors from the D-alanyl-Dalanine moiety to the D-alanyl-D-lactate depsipeptide is a key correlate of vancomycin resistance in Enterococcus faecium. Penicillin resistant clones of Streptococcus pneumoniae produce clone-specific altered cell walls in which the ratio of branched versus linear stempeptides varies with the particular resistant clone In Staphylococcus aureus carrying the mecA gene a cluster of additional genetic determinants - so called auxiliary genes or fem factors - is essential for the high level and homogeneous expression of resistance and several of these genes have recently been identified as genes controlling the biosynthesis of cell wall muropeptides.A cluster of auxiliary genes located on the large A fragment of the SmaI digested staphylococcal chromosome appears to be involved with the sequential addition of glycin units to the epsilon amino group of the lysine residues in the stem peptide of the wall precursors.Another large cluster of mutations -, identifiable by transposon mutagenesis -located on the I fragment results in a blockade of the synthesis of alanyl-glycine containing muropeptides.In yet another mutant, the ability of cells to normally amidate the alpha amino group of glutamate residues is impaired.Inactivation of any one of these sites - the number of which has now risen to well over ten and which are scattered over twothirds of the staphylococcal chromosome - results in reduction of methicillin resistance; production of a signature heterogeneous phenotype and abnormal cell wall peptidoglycan which is also characteristic of the particular mutant. All these properties cotrasfer during genetic back-crosses together with the unique physical location of the transposon insert.Auxiliary genes may be of widespread occurrance and may offer alternative targets for antibacterial agents.